[General]

The **Merck Manual** of Diagnosis and Therapy

Section 16. Cardiovascular Disorders

Chapter 199. Arterial **Hypertension**

*Arterial **hypertension**: Elevation of **systolic** and/or diastolic BP, either primary or secondary.*

(For a discussion of **hypertension** in pregnancy, see Ch. 250.)

Prevalence

It is estimated that there are nearly 50 million hypertensives in the USA (**systolic** BP >= 140 mm Hg and/or diastolic >= 90 mm Hg, or taking antihypertensive medication). For unknown reasons, the prevalence of **hypertension** seems to be decreasing in the USA (see Table 199-1). **Hypertension** occurs more often in black adults (32%) than in white (23%) or Mexican American (23%) adults, and morbidity and mortality are greater in blacks. Diastolic BP increases with age until age 55 or 60.

Prevalence of isolated **systolic hypertension** (ISH-- >= 140 mm Hg **systolic**, < 90 mm Hg diastolic) increases with age until at least age 80. If persons with ISH and diastolic **hypertension** are considered, > 50% of black and white men and > 60% of women over age 65 have **hypertension**. ISH is more prevalent among women than men in both races. Prevalence data, derived mainly from large screening programs such as the National Health and Nutrition Examination Survey, rely on one or more BP determinations made during one visit. Thus, these percentages are higher than they would be if BP had been measured over time (regression toward the mean). Between 85 and 90% of cases are primary (essential); in 5 or 10%, **hypertension** is secondary to bilateral renal parenchymal disease, and only 1 or 2% of cases are due to a potentially curable condition.

Etiology and Pathogenesis

- **Primary hypertension**: Primary (essential) **hypertension** is of unknown etiology; its diverse hemodynamic and pathophysiologic derangements are unlikely to result from a single cause. Heredity is a predisposing factor, but the exact mechanism is unclear. Environmental factors (eg, dietary Na, obesity, stress) seem to act only in genetically susceptible persons. Isolated, perfused kidneys from Dahl salt-sensitive rats (which are genetically prone to **hypertension** when fed a high-salt diet) do not excrete water or Na as rapidly as those from Dahl salt-resistant rats, even before **hypertension** develops.

The pathogenic mechanisms must lead to increased total peripheral vascular resistance (TPR) by inducing vasoconstriction, to increased cardiac output (CO), or to both because BP equals CO (flow) times resistance. Although expansion of intravascular and extravascular fluid volume is widely claimed to be important, such expansion can only raise BP by increasing CO (by increasing venous return to the heart), by increasing TPR (by causing vasoconstriction), or by both; it frequently does neither.

Abnormal Na transport across the cell wall due to a defect in or inhibition of the Na-K pump (Na^+,K^+-ATPase) or due to increased permeability to Na^+ has been described in some cases of **hypertension**. The net result is increased intracellular Na, which makes the cell more sensitive to sympathetic stimulation. Because Ca follows Na, it is postulated that the accumulation of intracellular Ca (and not Na per se) is responsible for the increased sensitivity. Na^+,K^+-ATPase may also be responsible for pumping norepinephrine back into the sympathetic neurons to inactivate this neurotransmitter. Thus, inhibition of this mechanism could conceivably enhance the effect of norepinephrine. Defects in Na transport have been described in normotensive children of hypertensive parents.

Stimulation of the sympathetic nervous system raises BP, usually more in hypertensive or prehypertensive patients than in normotensive patients. Whether this hyperresponsiveness resides in the sympathetic nervous system itself or in the myocardium and vascular smooth muscle that it innervates is unknown, but it can often be detected before sustained **hypertension** develops. A high resting pulse rate, which can be a manifestation of increased sympathetic nervous activity, is a well-known predictor of subsequent **hypertension**. Some hypertensive patients have a higher-than-normal circulating plasma catecholamine level at rest, especially early in clinical development.

Drugs that depress sympathetic nervous activity frequently reduce BP in patients with primary **hypertension**. However, this observation cannot be considered evidence for implicating the sympathetic nervous system as the causative factor in primary **hypertension**. In hypertensive patients, the baroreflexes tend to sustain rather than counteract **hypertension**, a phenomenon known as "resetting the barostats," which may be a result rather than a cause of **hypertension**. Some hypertensive patients have defective storage of norepinephrine, thus permitting more to circulate.

In the **renin-angiotensin-aldosterone system,** the juxtaglomerular apparatus helps regulate volume and pressure. Renin, a proteolytic enzyme formed in the granules of the juxtaglomerular apparatus cells, catalyzes conversion of the protein angiotensinogen to angiotensin I, a decapeptide. This inactive product is cleaved by a converting enzyme, mainly in the lung but also in the kidney and brain, to an octapeptide, angiotensin II, which is a potent vasoconstrictor that also stimulates release of aldosterone. Also found in the circulation, the des-ASP heptapeptide (angiotensin III) is as active as angiotensin II in stimulating aldosterone release but has much less pressor activity.

Renin secretion is controlled by at least four mechanisms that are not mutually exclusive: A renal vascular receptor responds to changes in tension in the afferent arteriolar wall; a

macula densa receptor detects changes in the delivery rate or concentration of NaCl in the distal tubule; circulating angiotensin has a negative feedback effect on renin secretion; and the sympathetic nervous system stimulates renin secretion via the renal nerve mediated by β receptors.

Plasma renin activity (PRA) is usually normal in patients with primary **hypertension** but is suppressed in about 25% and elevated in about 15%. **Hypertension** is more likely to be accompanied by low renin levels in blacks and the elderly. The accelerated (malignant) phase of **hypertension** is usually accompanied by elevated PRA (see Malignant Hypertensive Arteriolar Nephrosclerosis in Ch. 228). Although angiotensin is generally acknowledged to be responsible for renovascular **hypertension** (see below), at least in the early phase, there is no consensus regarding the role of the renin-angiotensin-aldosterone system in patients with primary **hypertension**, even in those with high PRA.

The mosaic theory states that multiple factors sustain elevated BP even though an aberration of only one was initially responsible; eg, the interaction between the sympathetic nervous system and the renin-angiotensin-aldosterone system. Sympathetic innervation of the juxtaglomerular apparatus in the kidney releases renin; angiotensin stimulates autonomic centers in the brain to increase sympathetic discharge. Angiotensin also stimulates production of aldosterone, which leads to Na retention; excessive intracellular Na enhances the reactivity of vascular smooth muscle to sympathetic stimulation.

Hypertension leads to more **hypertension**. Other mechanisms become involved when **hypertension** due to an identifiable cause (eg, catecholamine release from a pheochromocytoma, renin and angiotensin from renal artery stenosis, aldosterone from an adrenal cortical adenoma) has existed for some time. Smooth muscle cell hypertrophy and hyperplasia in the arterioles resulting from prolonged **hypertension** reduce the caliber of the lumen, thus increasing TPR. In addition, trivial shortening of hypertrophied smooth muscle in the thickened wall of an arteriole will reduce the radius of an already narrowed lumen to a much greater extent than if the muscle and lumen were normal. This may be why the longer **hypertension** has existed, the less likely surgery for secondary causes will restore BP to normal.

Deficiency of a vasodilator substance rather than excess of a vasoconstrictor (eg, angiotensin, norepinephrine) may cause **hypertension**. The kallikrein system, which produces the potent vasodilator bradykinin, is beginning to be studied. Extracts of renal medulla contain vasodilators, including a neutral lipid and a prostaglandin; absence of these vasodilators due to renal parenchymal disease or bilateral nephrectomy would permit BP to rise. Modest **hypertension** sensitive to Na and water balance is characteristic in anephric persons (renoprival **hypertension**).

Endothelial cells produce potent vasodilators (nitric oxide, prostacyclin) and the most potent vasoconstrictor, endothelin. Therefore, dysfunction of the endothelium could have a profound effect on BP. The endothelium's role in **hypertension** is being investigated. Evidence that hypertensive persons have decreased activity of nitric oxide is preliminary.

Secondary hypertension: Secondary **hypertension** is associated with renal parenchymal disease (eg, chronic glomerulonephritis or pyelonephritis, polycystic renal disease, collagen disease of the kidney, obstructive uropathy) or pheochromocytoma, Cushing's syndrome, primary aldosteronism, hyperthyroidism, myxedema, coarctation of the aorta, or renovascular disease (see Renovascular **Hypertension**, below). It may also be associated with the use of excessive alcohol, oral contraceptives, sympathomimetics, corticosteroids, cocaine, or licorice.

Hypertension associated with chronic renal parenchymal disease results from combination of a renin-dependent mechanism and a volume-dependent mechanism. In most cases, increased renin activity cannot be demonstrated in peripheral blood, and meticulous attention to fluid balance usually controls BP.

Diagnosis and treatment of secondary causes of **hypertension** are dealt with elsewhere in *The **Manual**.* The remainder of this discussion focuses almost entirely on primary **hypertension**.

Pathology

No early pathologic changes occur in primary **hypertension**. Ultimately, generalized arteriolar sclerosis develops; it is particularly apparent in the kidney (nephrosclerosis) and is characterized by medial hypertrophy and hyalinization. Nephrosclerosis is the hallmark of primary **hypertension**. Left ventricular hypertrophy and, eventually, dilation develop gradually. Coronary, cerebral, aortic, renal, and peripheral atherosclerosis are more common and more severe in hypertensives because **hypertension** accelerates atherogenesis. **Hypertension** is a more important risk factor for stroke than for atherosclerotic heart disease. Tiny Charcot-Bouchard aneurysms, frequently found in perforating arteries (especially in the basal ganglia) of hypertensives, may be the source of intracerebral hemorrhage.

Hemodynamics

Not all patients with primary **hypertension** have normal CO and increased TPR. CO is increased, and TPR is inappropriately normal for the level of CO in the early labile phase of primary **hypertension**. TPR increases and CO later returns to normal, probably because of autoregulation. Patients with high, fixed diastolic pressures often have decreased CO. The role of the large veins in the pathophysiology of primary **hypertension** has largely been ignored, but venoconstriction early in the disease may contribute to the increased CO.

Plasma volume tends to decrease as BP increases, although some patients have expanded plasma volumes. Hemodynamic, plasma volume, and PRA variations are evidence that primary **hypertension** is more than a single entity or that different mechanisms are involved in different stages of the disorder.

Renal blood flow gradually decreases as the diastolic BP increases and arteriolar sclerosis begins. GFR remains normal until late in the disease, and, as a result, the filtration fraction is increased. Coronary, cerebral, and muscle blood flow are maintained unless concomitant severe atherosclerosis is present in these vascular beds.

In the absence of heart failure, CO is normal or increased, and peripheral resistance is usually high in **hypertension** due to pheochromocytoma, primary aldosteronism, renal artery disease, and renal parenchymal disease. Plasma volume tends to be high in **hypertension** due to primary aldosteronism or renal parenchymal disease and may be subnormal in pheochromocytoma.

Systolic hypertension (with normal diastolic pressure) is not a discrete entity. It often results from increased CO or stroke volume (eg, labile phase of primary **hypertension**, thyrotoxicosis, arteriovenous fistula, aortic regurgitation); in elderly persons with normal or low CO, it usually reflects inelasticity of the aorta and its major branches (arteriosclerotic **hypertension**).

Symptoms and Signs

Primary **hypertension** is asymptomatic until complications develop in target organs (eg, left ventricular failure, atherosclerotic heart disease, cerebrovascular insufficiency with or without stroke, renal failure). However, the symptoms of hypertensive encephalopathy due to severe **hypertension** and cerebral edema are discussed below. Dizziness, flushed facies, headache, fatigue, epistaxis, and nervousness are not caused by uncomplicated **hypertension**.

A fourth heart sound and broad, notched P-wave abnormalities on the ECG are among the earliest signs of hypertensive heart disease. Echocardiographic evidence of left ventricular hypertrophy may appear later. Chest x-ray is often normal until the late dilated phase of hypertensive heart disease. Aortic dissection or leaking aneurysm of the aorta may be the first sign of **hypertension** or may complicate untreated **hypertension**. Polyuria, nocturia, diminished renal concentrating ability, proteinuria, microhematuria, cylindruria, and nitrogen retention are late manifestations of arteriolar nephrosclerosis.

Retinal changes may include retinal hemorrhages, exudates, papilledema, and vascular accidents. On the basis of retinal changes, Keith, Wagener, and Barker classified **hypertension** into groups that have important prognostic implications: group 1--constriction of retinal arterioles only; group 2--constriction and sclerosis of retinal arterioles; group 3--hemorrhages and exudates in addition to vascular changes; group 4 (malignant **hypertension**)--papilledema.

Diagnosis

Diagnosis of primary **hypertension** depends on repeatedly demonstrating higher-than-normal **systolic** and/or diastolic BP and excluding secondary causes.

At least two BP determinations should be taken on each of 3 days before a patient is diagnosed as hypertensive (see Table 199-2). More BP determinations are desirable for patients in the low **hypertension** range and especially for patients with markedly labile BP. Normal BP is much lower for infants and children (see Screening in Ch. 256). Sporadic higher levels in patients who have been resting for > 5 min suggest an unusual lability of BP that may precede sustained **hypertension**. For example, office or white coat **hypertension** refers to BP that is consistently elevated in the physician's office but normal when measured at home or by ambulatory BP monitoring.

The basic or minimal evaluation recommended for patients with **hypertension** includes history and physical examination, CBC, urinalysis, serum analysis (creatinine; K; Na; glucose; total, high density, and low density lipoprotein cholesterol), and ECG. The more severe the **hypertension** and the younger the patient, the more extensive the evaluation should be. Ambulatory BP monitoring, renal scintigraphy, chest x-ray, screening tests for pheochromocytoma, and renin-sodium profiling are not routinely necessary. Peripheral plasma renin activity has not been helpful in diagnosis or drug selection, but it may be an independent risk factor for coronary disease (but not for stroke or total cardiovascular mortality).

Pheochromocytoma (see also Ch. 9) secretes catecholamines, which, besides elevating BP, usually produce symptoms (various combinations of headache, palpitations, tachycardia, excessive perspiration, tremor, and pallor) that should alert the physician to this possibility. Catecholamines (eg, epinephrine, norepinephrine) are eventually metabolized in the body to a common product, 3-methoxy-4-hydroxymandelic acid, often called vanillylmandelic acid

(VMA). Diagnosis depends on demonstrating increased urinary or plasma concentrations of catecholamine or increased urinary concentrations of metanephrines and VMA.

Hypokalemia not due to diuretics should suggest **primary aldosteronism.** Proteinuria, cylindruria, or microhematuria with or without nitrogen retention early in the course of **hypertension** is strong evidence of underlying **primary renal disease.** Absent or markedly reduced and delayed femoral arterial pulses in a hypertensive patient aged < 30 yr are presumptive evidence of **coarctation of the aorta.** Cushing's syndrome, collagen disease, toxemia of pregnancy, acute porphyria, hyperthyroidism, myxedema, acromegaly, some CNS disorders, and primary aldosteronism must be excluded; these disorders are discussed elsewhere in *The **Manual**.*

Prognosis

An untreated hypertensive patient is at great risk of disabling or fatal left ventricular failure, MI, cerebral hemorrhage or infarction, or renal failure at an early age. **Hypertension** is the most important risk factor predisposing to stroke. It is one of three risk factors (along with cigarette smoking and hypercholesterolemia) predisposing to coronary atherosclerosis. The higher the BP and the more severe the changes in the retina, the worse the prognosis. Fewer than 5% of patients with group 4 or malignant **hypertension** characterized by papilledema and < 10% of patients with group 3 changes in the fundus survive 1 yr without treatment. Effective medical control of **hypertension** will prevent or forestall most complications and will prolong life in patients with ISH or diastolic **hypertension**. Coronary artery disease is the most common cause of death among treated hypertensive patients. **Systolic** BP is a more important predictor of fatal and nonfatal cardiovascular events than diastolic BP. In a follow-up of men screened for the Multiple Risk Factor Intervention Trial, overall mortality was related to **systolic** BP, regardless of diastolic BP.

Treatment

Primary **hypertension** has no cure, but treatment can modify its course. It is estimated that only 24% of hypertensive patients in the USA have their BP controlled to < 140/90 mm Hg, and 30% are unaware that they have **hypertension**.

Lifestyle modifications: Extra rest, prolonged vacations, moderate weight reduction, and dietary Na restriction are not as effective as antihypertensive drug therapy. Patients with uncomplicated **hypertension** need not restrict their activities as long as their BP is controlled. Dietary restrictions can help control diabetes mellitus, obesity, and blood lipid abnormalities. In stage 1 **hypertension**, weight reduction to ideal levels, modest dietary Na restriction to < 2 g/day, and alcohol consumption to < 1 oz/day may make drug therapy unnecessary. Prudent exercise should be encouraged. Smoking should be unambiguously discouraged.

Antihypertensive drug therapy: Most authorities would agree that patients with **systolic** BP averaging 140 to 159 mm Hg and/or diastolic BP of 90 to 94 mm Hg should receive antihypertensive drugs if lifestyle modifications do not normalize BP. The benefit of drug therapy for patients with stage 1 **hypertension** is unequivocal. There are no data on the efficacy of antihypertensive therapy for borderline **hypertension**. When target organ damage or other risk factors are present, or when the **systolic** BP is >= 160 mm Hg and/or diastolic BP is >= 100 mm Hg, drug therapy should not be deferred to await the uncertain results of lifestyle modifications. Heart failure, symptomatic coronary atherosclerosis, cerebrovascular disease, and renal failure require urgent and judicious antihypertensive therapy.

The **Systolic Hypertension** in the Elderly Trial showed marked benefit from antihypertensive treatment. In patients >= 60 yr with **systolic** BP >= 160 and diastolic BP < 90 mm Hg, chlorthalidone (plus atenolol, if necessary) reduced the incidence of stroke (by 36%) and other major cardiovascular events. Benefit was found in both young elderly and old elderly. The goal was to lower **systolic** BP to < 160 mm Hg and by at least 20 mm Hg for patients whose pretreatment **systolic** BP was 160 to 179 mm Hg.

Except in patients > 65 yr, the goal of therapy should be to reduce BP to < 135/80 mm Hg or as near to this level as tolerable. Retrospective studies indicate that coronary mortality may increase if diastolic BP is reduced to < 85 mm Hg, especially for patients with clinical evidence of preexisting atherosclerotic heart disease (the so-called J curve). However, other observations have failed to confirm this, and most reports have failed to show a J curve for **systolic** BP, even when a J curve in diastolic BP was observed. Usually, it is advantageous to have the patient measure BP at home, provided that the patient or a family member is thoroughly instructed and closely monitored and the sphygmomanometer is carefully calibrated at regular intervals.

Drug therapy should be initiated with a diuretic or a β-blocker, unless these drugs are contraindicated or another class of drugs is indicated. If these drugs are ineffective, alternative classes suitable for initial therapy include Ca blockers, ACE inhibitors, angiotensin II receptor blockers, α_1-adrenergic blockers, and α-β-blockers (see Table 199-3). However, none of these except nitrendipine, a dihydropyridine Ca blocker, has been shown to reduce cardiovascular morbidity and mortality in prospective, randomized trials, whereas diuretics or β-blockers as initial therapy have shown beneficial effects on cardiovascular and cerebrovascular morbidity and mortality. Nitrendipine significantly reduced fatal and nonfatal strokes but not coronary events in elderly patients with isolated **systolic hypertension**.

Selection of the initial drug should be guided by age and race of the patient and by coexisting diseases or conditions that may represent a contraindication for certain drugs (eg, asthma and β-blockers) or a special indication for certain drugs (eg, angina pectoris and β-blockers or Ca blockers). In the Veterans Administration Trial of single drug therapy for **hypertension** in men, black patients responded best to a Ca blocker (diltiazem). Hydrochlorothiazide was more effective in white or black men aged > 60 yr than in younger patients. The β-blocker atenolol was more effective in white patients than in blacks, regardless of age. Race and age are only guidelines to which there are many exceptions.

If the initial drug is ineffective or causes intolerable adverse effects, another can be substituted (sequential monotherapy). Alternatively, if the original drug is only partially effective but well tolerated, the dose may be increased or a second drug can be added, which should be of a different class (stepped care). The central-acting sympathetic inhibiting drugs are not recommended for initial therapy because of their high adverse effect profile. However, they are effective and can be used in small doses in combination regimens. A direct vasodilator (hydralazine or minoxidil) may be used with a diuretic to prevent fluid retention and with a β-blocker to prevent reflex tachycardia.

Preferably, treatment is started with only one drug unless **hypertension** is severe. However, combinations of a diuretic with a β-blocker or an ACE inhibitor are available in single tablets in subtherapeutic doses of each compound that together have an antihypertensive effect with minimal adverse effects. Two of these combinations are available in the USA for initial therapy of stage 1 or 2 **hypertension** (see Table 199-4). Three or four drugs in combination may be necessary for severe or resistant **hypertension**.

All thiazide derivatives and their congeners are equally effective in equivalent doses (see Table 199-5). Metolazone, indapamide, and the loop diuretics furosemide, bumetanide, ethacrynic acid, and torsemide are no more effective than the thiazides but are preferred in patients with chronic renal failure. The antihypertensive action of diuretics seems to be due to a modest reduction in plasma volume and a decrease in vascular reactivity, possibly mediated by shifts in Na from intracellular to extracellular loci.

K supplementation or the use of a K-sparing diuretic is recommended with kaliuretic diuretics for patients who are also taking digitalis, have known heart disease, have an abnormal ECG, have ectopy or arrhythmias, or develop ectopy or arrhythmias while taking the diuretic. The K-sparing distal tubular diuretics (spironolactone, triamterene, amiloride) do not cause hypokalemia, hyperuricemia, or hyperglycemia, but they are not as effective as the thiazides in controlling **hypertension**. Instead of K supplementation, spironolactone 25 to 100 mg/day, triamterene 50 to 150 mg/day, or amiloride 5 to 10 mg/day can be added to thiazide therapy to treat or prevent hypokalemia.

A disadvantage of diuretics is sexual dysfunction, which occurs more commonly than with some of the other drugs proposed for initial therapy. Metabolic adverse effects of diuretics (hypokalemia, hypomagnesemia, hyperuricemia, hyperglycemia, hypercalcemia, hyperlipidemia) are dose-related and, if properly managed, do not usually prevent diuretic use. Spironolactone can cause breast tenderness, making amiloride or triamterene preferable when a K-sparing drug is chosen for males.

Diuretics uncommonly precipitate clinical type II diabetes or aggravate preexisting type II diabetes in susceptible patients. Most diabetics can tolerate a low-dose thiazide diuretic with little or no effect on the control of their diabetes, although it may aggravate hyperinsulinemia. Exercise and weight loss will ameliorate but not eliminate these adverse effects.

Thiazide and related diuretics can increase serum cholesterol (mostly in the low-density lipoprotein fraction) and triglyceride concentration, although most long-term studies failed to show an adverse effect at > 1 yr. Furthermore, increased concentration seems to occur only in susceptible patients, is apparent within 4 wk of treatment, and can be ameliorated by a low-fat diet. Elevated concentration of serum cholesterol or triglycerides is not an a priori contraindication to the use of diuretics in the management of **hypertension**, because the lipidemic effect is more likely to occur in patients with normal concentrations than in patients with hyperlipidemia.

A hereditary predisposition probably explains the few cases in which diuretic-induced hyperuricemia has led to clinical gout. The **Hypertension** Detection and Follow-Up Program recorded only 15 cases of gout in 5 yr among 3693 participants at risk. Diuretic-induced hyperuricemia in the absence of gout is not an indication for antiuricemic therapy, nor does it contraindicate continued diuretic use. Diuretics are less expensive than the alternatives for initial therapy.

All **β-blockers** (see Table 199-6) are equivalent in terms of antihypertensive efficacy. If the patient also has diabetes mellitus, chronic occlusive peripheral arterial disease, or COPD, it is preferable to use a cardioselective β-blocker (acebutolol, atenolol, betaxolol, bisoprolol, metoprolol). However, cardioselectivity is only relative and diminishes as the dose of the β-blocker increases. Even cardioselective β-blockers are contraindicated in the presence of severe asthma or COPD with a prominent bronchospastic component. Use of a cardioselective β-blocker in the absence of one of these indications offers no advantage over nonselective β-blockers.

β-Blockers with intrinsic sympathomimetic activity (ISA--eg, acebutolol, carteolol, penbutolol, pindolol) do not have an adverse effect on serum lipids; they are also less likely to produce severe bradycardia than are non-ISA β-blockers. However, asymptomatic sinus bradycardia, even with rates in the 40s, usually is not harmful.

β-Blockers without ISA and without α-blocking properties have a cardioprotective effect for patients who have had an MI; these drugs are thus indicated for such hypertensive patients.

Disadvantages of β-blockers include a high incidence of CNS adverse effects (sleep disturbances, fatigue, lethargy) and contraindications (greater than first-degree heart block, asthma, sick sinus syndrome, heart failure). Similar to diuretics, β-blockers can cause sexual dysfunction in men and metabolic adverse effects, including impaired glucose tolerance, depressed high density lipoprotein cholesterol, and increased serum total cholesterol and triglyceride concentrations.

Similar to ISA β-blockers, the α-β-blocker labetalol does not reduce resting pulse rate as much as the non-ISA β-blockers and does not seem to have an adverse effect on serum lipids.

Ca blockers (see Table 199-7) are potent peripheral vasodilators and reduce BP by decreasing TPR. The diphenylalkylamine derivative verapamil and the benzothiazepine derivative diltiazem slow the heart rate, decrease atrioventricular conduction, and have a negative inotropic effect on myocardial contractility, similar to β-blockers. Consequently, they should not be prescribed for patients with greater than first-degree heart block or left ventricular failure. In general, β-blockers and verapamil or diltiazem should not be prescribed in the same regimen for patients with left ventricular dysfunction.

The dihydropyridine derivatives (amlodipine, felodipine, isradipine, nicardipine, nifedipine, nisoldipine) have a lesser negative inotropic effect than the nondihydropyridines but can sometimes cause reflexive tachycardia. These drugs are more potent peripheral vasodilators than are the nondihydropyridines and should therefore be more effective. However, in long-term antihypertensive therapy, they do not seem to be more potent than nondihydropyridine Ca blockers.

Short-acting nifedipine has been associated in nonrandomized case-control and cohort studies with increased rates of MI compared with other classes of drugs and therefore should not be used to treat **hypertension** (for which it is not indicated). Short-acting diltiazem also is not indicated for treating **hypertension**. Long-acting Ca blockers are preferred.

A Ca blocker is preferred to a β-blocker for hypertensive patients with angina pectoris who also have bronchospastic disease or Raynaud's disease.

Ca blockers do not have metabolic adverse effects, but they can be more expensive than ACE inhibitors.

ACE inhibitors (see Table 199-8) are vasodilators that reduce BP by interfering with the generation of angiotensin II from angiotensin I and by inhibiting the degradation of bradykinin, thereby decreasing peripheral vascular resistance without inciting reflex tachycardia. They reduce BP in many hypertensive patients, regardless of plasma renin activity.

One of the advantages of ACE inhibitors in the management of **hypertension** is the low adverse effect profile. A dry irritating cough is the most frequent adverse effect. ACE

inhibitors do not adversely affect serum lipids, plasma glucose, or uric acid. They tend to increase serum K, especially in patients with chronic renal failure or in patients taking K-sparing diuretics, K supplements, or NSAIDs. These drugs are least likely to cause sexual dysfunction in males. Angioedema is a rare adverse effect of ACE inhibitors and can be life-threatening if it involves the oropharyngeal area.

ACE inhibitors reduce proteinuria for patients with diabetic nephropathy and may retard glomerulosclerosis by selectively dilating the efferent (postglomerular) arteriole, thus reducing glomerular capillary pressure without compromising blood flow. They retard the loss of renal function in patients with nephropathy due to type I diabetes. If ACE inhibitors are prescribed for patients with chronic renal disease, especially when azotemia is present, serum creatinine and K levels should be monitored frequently. ACE inhibitors can cause acute renal failure in patients who have severe bilateral renal artery stenosis or severe stenosis in the artery to a solitary kidney, presumably because under these conditions GFR is maintained by angiotensin II-mediated constriction of the efferent arteriole, which is abolished by ACE inhibition. For the same reason, they can cause acute renal failure in hypovolemic patients and in patients with severe heart failure. Nevertheless, ACE inhibitors reduce mortality and re-hospitalization rates for patients with left ventricular dysfunction and ejection fractions < 40%.

Diuretics consistently enhance the antihypertensive activity of ACE inhibitors as much as, if not more than, they do for any other class of antihypertensive drugs.

A disadvantage of treatment with ACE inhibitors is expense.

Angiotensin II receptor blockers (see Table 199-8) block angiotensin II receptors and therefore interfere with the renin-angiotensin system, perhaps more completely than do the ACE inhibitors. They do not block the degradation of bradykinin, which perhaps explains why they do not cause a dry irritating cough. To the extent that bradykinin may contribute to the hypotensive effect of ACE inhibitors, the angiotensin II receptor blockers may less effectively reduce BP. However, to the extent that tissue ACE is not blocked by ACE inhibitors, angiotensin II receptor blockers may more effectively reduce BP. Studies have shown that they are equally effective as antihypertensive drugs. Angiotensin II receptor blockers seem to be remarkably free of adverse effects and have been implicated in fewer cases of angioedema than have the ACE inhibitors, but this adverse effect is very rare with either class of drugs. Presumably, angiotensin II receptor blockers have the same beneficial effects as ACE inhibitors in patients with left ventricular failure and in type I diabetics with nephropathy, but definitive controlled trials have not been reported. Precautions for the use of ACE inhibitors in patients with renovascular **hypertension**, hypovolemia, and severe heart failure also apply to the angiotensin II receptor blockers.

Adrenergic inhibitors (see Table 199-9) include α_2 agonists, which have a central action and are more likely than other drugs to produce drowsiness, lethargy, and sometimes depression. Methyldopa, clonidine, guanabenz, and guanfacine reduce sympathetic nervous activity by stimulating the presynaptic α_2-adrenergic receptors in the brain stem. Clonidine is available for transdermal administration in 2.5-, 5-, or 7.5-mg impregnated patches applied once weekly, delivering respectively 0.1, 0.2, or 0.3 mg/day. This unique dosage form seems to be as effective as the oral route with fewer adverse effects. However, about 20% of patients develop cutaneous reactions at the site of application, requiring discontinuation of the drug in this form.

Prazosin, terazosin, and doxazosin are peripheral **postsynaptic α_1-adrenergic blockers** that act on veins and arterioles. They all relieve symptoms of benign prostatic hyperplasia

and are the only group of antihypertensive drugs that have a modest effect on reducing serum cholesterol, especially the low density lipoprotein fraction.

Guanethidine and guanadrel block sympathetic transmission at the neuroeffector junction and, similar to reserpine, deplete tissue stores of norepinephrine. Guanethidine, in particular, is potent but difficult to titrate, so it has largely been discontinued with the advent of newer drugs. Guanadrel is a shorter-acting drug than guanethidine and produces fewer adverse effects. Reserpine depletes the brain of norepinephrine and serotonin and also depletes the peripheral sympathetic nerve terminals of norepinephrine. Except for α_1 receptor blockers, these adrenergic blockers are not recommended for routine initial therapy because they may cause subtle fluid retention, leading to pseudotolerance, and they also have higher adverse effect profiles than the drugs recommended for step 1. However, α_2-agonists and reserpine are excellent step-2 drugs, especially when used with a diuretic.

The mechanism of **direct vasodilators** (independent of the autonomic nervous system) is different from that of Ca blockers and ACE inhibitors (see Table 199-11): Minoxidil is more potent than hydralazine but is associated with more adverse effects, including Na and water retention and hirsutism, which is poorly tolerated by women; it should be reserved for severe, resistant **hypertension**. Hydralazine has long been used as (and remains) a step-3 drug because its antihypertensive effect is additive to that of other vasodilating drugs. The lupus syndrome is rarely observed if the dosage is < 300 mg/day.

Vasodilating prostaglandins and compounds that enhance endothelial production of nitric oxide, depress endothelial release of endothelin, or block endothelin receptors may offer new possibilities in treating **hypertension**.

Drug treatment of hypertensive emergencies: Hypertensive crises may be classified as true emergencies requiring immediate reduction of BP (eg, hypertensive encephalopathy, acute left ventricular failure with pulmonary edema, eclampsia, acute aortic dissection, severe **hypertension** accompanying unstable angina or acute MI), usually with parenteral drugs (see Table 199-10), or hypertensive urgencies in which the physician is more concerned than the patient. Hypertensive urgencies are frequently overtreated.

Prompt BP reduction with parenteral drugs is indicated for patients with hypertensive encephalopathy, acute left ventricular failure, or other true emergencies. IV diazoxide, sodium nitroprusside, nitroglycerin, nicardipine, or labetalol is usually used for this purpose. Because diazoxide is a nondiuretic thiazide derivative that can cause fluid retention, furosemide 40 or 80 mg IV is usually given with it. Diazoxide is administered by rapid IV injections of 50 to 100 mg (1 to 1.5 mg/kg, <= 100 mg/dose) given q 5 to 10 min until the BP reaches the optimal level. Adverse effects include nausea, vomiting, hyperglycemia, hyperuricemia, tachycardia, and, only occasionally, hypotension (generally without shock).

Sodium nitroprusside 0.25 to 10 μg/kg/min (for <= 10 min at the highest dose to minimize the risk of cyanide toxicity) given by continuous IV infusion in 5% D/W can promptly reduce BP in a hypertensive crisis, but its evanescent effect and potency require almost continuous monitoring of BP in an ICU. Unlike diazoxide, it produces venodilation and arteriolar dilation and therefore reduces preload and afterload, making it especially useful for managing hypertensive patients with heart failure. Adverse effects include nausea, vomiting, agitation, muscular twitching, and cutis anserina (goose flesh) if BP is reduced too rapidly. Acute psychosis from thiocyanate intoxication can result from prolonged therapy, especially in patients with renal failure. The drug should be discontinued if the serum thiocyanate concentration is > 12 mg/dL (206 μmol/dL).

Nitroglycerin, similar to sodium nitroprusside, relaxes the resistance vessels and the large capacitance veins. Compared with sodium nitroprusside, it has a greater effect on veins than on arterioles. IV infusions of nitroglycerin have been used to manage **hypertension** during and after coronary bypass, heart failure, acute MI, unstable angina pectoris, and acute pulmonary edema. Hemodynamic studies indicate that IV nitroglycerin is preferable to sodium nitroprusside in managing **hypertension** associated with severe coronary disease because it increases coronary flow, whereas sodium nitroprusside tends to decrease coronary flow to ischemic areas, possibly because of a "steal" mechanism. The most frequent adverse reaction is headache, which occurs in about 2% of patients; tachycardia, nausea, vomiting, apprehension, restlessness, muscular twitching, and palpitations have also been observed.

Labetalol 20 to 40 mg IV q 10 min or as an infusion is as effective as nitroprusside, diazoxide, or nitroglycerin in managing hypertensive crises. Serious hypotensive episodes have not been observed when labetalol is given by this method, and adverse effects have been minimal. Because of its β-blocking activity, labetalol should probably not be used for hypertensive emergencies in patients with acute left ventricular failure or in asthmatic patients.

Although short-acting nifedipine given orally usually reduces BP rapidly, it has been associated with acute cardiovascular and cerebrovascular events (sometimes fatal) and is not recommended for treating hypertensive emergencies or urgencies. It is not indicated for managing **hypertension**.

Back to top of page